

### **REMARKS**

Claims 21-25 are now pending for the Examiner's consideration.

Applicants respectfully request reconsideration of the pending claims in light of the following remarks.

#### **Rejection based on 35 USC §112 first paragraph**

Claims 21-25 were rejected under 35 U.S.C. § 112 first paragraph, for the reasons set forth on pages 2-4 of the Office Action. Applicants note that claims 21-25 are only direct to a method of treating cancer, not preventing cancer. Applicants believe that the rejection thus does not apply and request that it be withdrawn.

#### **Rejection based on 35 USC §103(a)**

Claims 21-25 were rejected under 35 U.S.C. § 103(a) over Tang et al. and Hawley et al., in vie of Goodman and Gilman for the reasons set forth on pages 4-7 of the Office Action. Applicants note that the current application provides experimental data that demonstrated unexpected and/or synergistic results with regard to the combination of Compound 1 with Docetaxel in breast cancer, Compound 1 with 5-FU in breast cancer, Compound 1 with Doxorubicin in breast cancer, Compound 1 with Cisplatin in small cell lung cancer, and Compound 1 with CTP-11 in colon cancer. The unexpected and / or synergistic results are described in biological examples 1 to 8.

Compound 1 with docetaxel: "Synergistic and / or unexpected" effect of the combination therapy of Compound 1 with docetaxel is shown in Biological Example 1. In Table 1, it is shown that when mice were treated with the combination of Compound 1 (40 QD to end) and docetaxel (5 QWK x 3), inhibition effect was 75% comparing to when mice were treated with Compound 1 alone (40 QD to end) and 82% when comparing to when mice were treated with docetaxel alone (5 QWK x 3). This is unexpected / synergistic effect because when mice were treated with docetaxel (5 QWK x3) alone, there was no tumor inhibition effects comparing to vehicle control and thus an *addictive effect* of Compound 1 (40 QD to end) and docetaxel (5 QWK x3) should be 0% comparing to Compound 1 (40 QD to end) and 53% comparing to docetaxel (5 QWK x 3).

"Synergistic and / or unexpected" effect is also shown in Table 1 by the combination therapy of Compound 1 (40 QD to end) and docetaxel (10 QWK x 3 of). The combination showed a 78% inhibition comparing to when the mice were treated with Compound 1 alone (40 QD to end). This means the net effect (78% inhibition) of docetaxel on mice already treated with Compound 1, is greater than the effect of docetaxel on mice alone (60% inhibition). Similarly, the net effect of compound 1 on mice already treated with docetaxel is 62% inhibition, which is greater that the 53% inhibition effect that compound 1 on mice alone.

Similarly, "synergistic and / or unexpected" is showed by the combination of Compound 1 (40 QD to end) and docetaxel (15 QWK x 3). The combination provided 82% inhibition

comparing to when the mice were treated with docetaxel alone. Therefore, the “net effect” (82% inhibition) of Compound 1 had on mice already treated with docetaxel (10 QWK x3) was greater than the effect of Compound 1 had on the mice alone (53% inhibition)

Compound 1 with 5-Fu: “synergistic and / or unexpected” effect for the combination therapy of Compound 1 with 5-Fu is also shown in Biological Example 3. In Table 3, Compound 1 alone provided a 57% inhibition comparing to control, and 5-Fu provided a 45% inhibitor comparing to the control. The combination provided 78% inhibition comparing to Compound 1. This 78% is greater than the previous 45%, which means the net effect of 5-Fu on mice which had already been treated with Compound 1, was greater than the net effect of 5-Fu on mice alone. Similarly, the combination provided a 76% inhibitor comparing to 5-Fu. This means the net effect of Compound 1 on mice which had been already treated with 5-Fu (76%) was greater than the net effect of Compound 1 on mice alone (57%).

Compound 1 with Doxorubicin: Similarly, “synergistic and / or unexpected” effect of the combination therapy of Compound 1 with Doxorubicin is shown in Biological Example 4. Similar analysis of the above applies.

Compound 1 with Cisplatin: “synergistic and / or unexpected” effect is also shown for the combination therapy of Compound 1 with Cisplatin in Biological Example 5. In Table 5, Compound 1 alone delayed the tumor volume to reach 900mm<sup>3</sup> by 11 days when compared to Vehicle. Cisplatin alone delayed the tumor volume to reach 900m<sup>3</sup> by 18 days when comparing to Vehicle. The combination of Compound 1 and Cisplatin delay tumor volume to reach 900m<sup>3</sup> by 40 days. This 40 days is greater than the sum of 11 days and 18 days. Therefore, we believe “synergistic / unexpected” effect is shown.

Compound 1 with Irinotecan (CPT-11): “synergistic and / or unexpected” effect of Compound 1 with Irinotecan is shown in Biological Example 7. In Table 7, the net effect of combination therapy of 20 QD to end of Compound 1 with (100) QWK x 3 of Irinotecan over Compound 1 alone (73.4%) or over Irinotecan alone (50.9%) is higher than the net effect Irinotecan (63.6%) alone or Compound 1 alone (34.9%). Following the same reasons as the above in Biological Examples 1 and 3, “synergistic” effect is shown.

Applicants thus request that the rejection be withdrawn.

**Conclusion**

In light of the preceding remarks, Applicants believe that all pending claims are now in condition for allowance. Applicants request that a Notice of Allowance be issued timely. If the above remarks are not to the satisfaction of the Examiner, Applicants invite the Examiner to contact the undersigned. If any fees other than those submitted herewith are due in connection with this response, including the fee for any required extension of time (for which Applicant hereby petitions), please charge such fees to Deposit Account No. 16-1445.

Respectfully submitted,

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